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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,000	SUCK ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-23* is/are pending in the application.

4a) Of the above claim(s) *7-11,16 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-6, 12-15, 17, 22-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 04/09/2008 is acknowledged.

2. Claims 1 and 4-23 are pending.

3. Claims 7-11, 16 and 18-21 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/17/2007.

4. Claims 1, 4-6, 12-15, 17 and 22-23 are currently under examination as they read on a Phl p 1 variant characterizes in that it has an additional cysteine residue as compared with the wild type.

Claim Objections

5. Claim 23 is objected to because of the following informalities:

The term "calim" in claim 23, line, 2 is misspelled and should be changed to "claim."

Appropriate correction is required.

6. The following new grounds of rejection are necessitated by the amendment filed on 04/09/2008.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 4 stands rejected and claims 1, 5-6, 12-15, 17 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the polypeptide variant rPHL p 1-A236C" in claim 6. There is insufficient antecedent basis for this limitation in the claim.

Claims 1, 4 and 22 recite specific allergen variants by amino acids residues making the claims indefinite. An inserted reference sequence identification number to show exactly where the mutants are different from the reference sequence would make the claims definite. The claims lack the requisite structural features for the composition.

The term "higher" in claims 1 and 22 is a relative term which renders the claim indefinite. The term "higher" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant's arguments filed on 04/09/2008 have been fully considered, but are not found persuasive.

Applicant argues:

> "The contention that the instant claims "lack requisite structural features for the claimed composition" is respectfully traversed insofar as the primary structure of the wild-type Phl p 1 polypeptide was appreciated in the art before the filing date of the instant application. See, for example, page 3, lines 19-27 of Applicants' own specification and the disclosure contained in Petersen et al. *(J. Allergy Clin. Immunol.* 95,987-994, 1995; PUBMED ID: 7751520). Based on this disclosure, a skilled artisan can readily obtain information pertaining to the polypeptide and/or polynucleotide sequence for wild-type Phl p 1. See, CITEXPLORE results which are enclosed herewith in Exhibit A. For example, it can be readily understood that UniProt accession No. Q40967 relates to *Phleumpretense* pollen allergen, while mRNA sequence has the EMBL accession No. Z27090 (formerly, PPRPHLP1X). Printouts of these sequences are enclosed herewith for the Examiner's review.
>
> The requirement that the claims explicitly recite sequence identifier number(s) of the polypeptides claimed herein is thus unnecessary. A skilled artisan can readily determine both the nature (i.e., mutant or wild-type) as well as the structure (i.e., amino acid sequence) of the rPhl pl species claimed herein. See, *Capon v. Eshhar v. Dudas,* (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078 (discussed *infra).*
>
> With respect to the alleged indefiniteness caused by the claim term "higher" and the rejection under § 112 based thereon, it is respectfully submitted that in view of the express knowledge of the wild-type Phl p 1 polypeptide sequence, coupled with a skilled worker's understanding of the structural characteristics of proteins, the metes and bounds of the claimed subject matter is well-understood by one of ordinary skill in the art. Withdrawal of the rejection is respectfully requested."

It remains the Examiner's position that it is indefinite to name specific amino acid position numbers in a protein without identifying the protein sequence. Natural variants of proteins exist and the addition or subtraction of just one amino acid will completely change the position number. Further, the claims are directed to polypeptide variants, which include Phl p1 having any number of truncations, additions, subtractions and/or substitutions. Therefore, referring to a specific position number in the broad genus of variants encompassed by the instant recitation is also indefinite.

It also remains the Examiner's position that "higher" in claims 1 and 22 is a relative term which renders the claim indefinite as the term "higher" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. One of ordinary skill in the art would not be reasonably apprised of the scope of the invention because "higher" can refer to both upstream and down stream amino acids residues and the direction of numbering is not an inherent feature of the variant.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 4-6, 12-15 and 17 stand rejected and claims 22-23 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: the polypeptide of SEQ ID NO:2, does not provide reasonable enablement for: a **polypeptide variant of the major allergen Phl p 1 from timothy grass**, which comprises **an additional Cys residue compared with the wild type Phl p 1 sequence** wherein the location of **said additional Cys residue** is higher than amino acid position 230 of said **wild type Phl p sequence** of claim 1; wherein the **additional Cys residue** is located between amino acid positions 230 and 240 of claim 4; wherein the **additional Cys residue** originates from **an amino acid exchange** of claim 5; the **polypeptide variant variant rPhl p 1-A236C** according to claim 1, which comprises a polypeptide sequence set forth in SEQ ID NO:2, wherein the additional Cys residue has been

introduced by exchange of Ala 236 of claim 6; The **polypeptide variant** of claim 1 which exists in various fold forms of claim 12; A fold form rPhl p 1-LM of the **polypeptide variant** according to claim 1, which is obtainable by (a) overexpressing in a host organism, a fusion protein comprising the **rPhl p 1 polypeptide variant** and a His tag; (b) denaturing inclusion bodies isolated from the host organism using guanidinium chloride; (c) renaturing of the dissolved protein on a chelate affinity chromatography column; (d) removing of the His tag, (e) employing gel filtration, (f) further purifying using chelate affinity chromatography, (g) isolating of the target protein from the flow-through; and (h) further employing gel filtration of claim 13; Fold form rPhl p 1-HM of **the allergen variant according** to claim 1 obtainable by (a) overexpressing in a host organism, a fusion protein comprising **the rPhl p 1 polypeptide variant** and a His tag; (b) denaturing inclusion bodies isolated from the host organism using guanidinium chloride; (c) renaturing of the dissolved protein on a chelate affinity chromatography column; (d) removing of the His tag, (e) employing gel filtration, (f) further purifying using chelate affinity chromatography, (g) eluting the target protein with an imidazole gradient; and (h) further employing gel filtration of claim 14; A **vaccine** which comprises **the polypeptide variant** according to claim 1 and an acceptable carrier of claim 15; and a **pharmaceutical composition** comprising **a polypeptides variant** according to claim 1 and a pharmaceutically acceptable carrier of claim 17; a **polypeptide variant** of major allergen Phl p 1 from timothy grass which comprises an additional Cys residue compared to the **wild type Phl p 1 sequence**, wherein the location of said additional Cys residue is higher than amino acid position 140 of said **wild-type sequence** of claim 22; which is (a) polypeptide which is encoded by a polynucleotide comprising the sequence set forth in SEQ ID NO:1; or (b) a polypeptide

which comprises the sequence set forth in SEQ ID NO:2 of claim 23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons as set forth in the Office Action mailed on 10/09/2007.

The specification has only disclosed the Phl p 1 allergen mutant consisting of SEQ ID NO:2.

The specification has not adequately disclosed any variant of the Phl p 1 molecule having any number of additions, deletions and substitutions as encompassed by the present claim recitations. The specification has provided no guidance or examples as to which allergen variants with an additional cysteine would work in the claimed invention other than the Phl p 1 allergen variant of SEQ ID NO:2. The term "variant" of a 240 amino acid protein with substitutions to any amino acid with any of the 20 naturally occurring amino acids, additions of any number of undisclosed amino acids in any position, deletion of any number of amino acids, or combinations thereof, literally results in billions of compounds. One of ordinary skill in the art would be required to perform undue experimentation to determine which allergen variants other than the allergen variant of SEQ ID NO:2 would work in the claimed invention.

The specification has also adequately disclosed any Phl p 1 allergen mutant having an additional cysteine residue as a result of an amino acid exchange of any amino acid. Further, the

specification does not adequately disclose any Phl p 1 allergen mutant having an additional cysteine residue as a result of the addition of a cysteine residue anywhere within the Phl p 1 molecule. The specification describes that the claimed allergen mutant may be used in a pharmaceutical composition for the treatment of allergies. However, the art shows that the addition of a cysteine molecule within an allergen does not always decrease IgE binding. In particular, see Schramm et al. (PTO-892, Reference V) teaches that surprisingly an allergen mutant of Phl p 5b with an additional cysteine residue does not decrease IgE binding even though the additional cysteine changes the conformation of the Phl p 5 molecule by the formation of a disulfide bond with another already present cysteine (In particular, page 2409, paragraph spanning left and right columns; page 2413, first paragraph, whole document). Therefore, because of this unpredictability, one of ordinary skill in the art would be required to perform undue experimentation to practice the claimed invention commensurate in scope with the claims.

Further, without reference to a specific sequence for the wild type, it is unclear which amino acid positions within the wild type are not currently cysteines. The wild type any naturally occurring variant of Phl p 1, including as yet unknown variants.

Also at issue is whether or not the claimed composition comprising an allergen variant would function as vaccine and pharmaceutical composition. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition as claimed, absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical compositions are effective for in vivo use, and the

lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Applicant's arguments filed on 04/09/2008 have been fully considered, but are not found persuasive.

Applicant argues:

> "At the outset, it is respectfully submitted that the lack of enablement rejection with respect to the variant of Phl p 1 is moot in view of the aforementioned arguments and/or amendments. With respect to variants of the claimed polypeptides, the PTO's contention is respectfully traversed. Applicants' specification, further in view of the art knowledge of Phl p 1 allergens and sequences (as substantiated by the references cited therein), provides a detailed description of the structure/activity of the claimed molecules. Structures (for example, amino acid sequences) of the claimed Phl p 1 species are recited in the instant sequence disclosure, further in view of the references cited in page 3 of the present specification. See, for example, the cDNA/polypeptide sequences disclosed in aforementioned reference by Petersen et al. It is now well-settled that a specification need not disclose, and preferably omits, what is well known to those skilled in the art when an application is filed (for example, with respect to the sequence of Phl p 1 species and/or variants thereof). See, e.g., *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a). Indeed, the Federal Circuit found that an application, which failed to disclose the amino acid sequence of a claimed protein, was not deficient in the written description requirement, despite the fact that the undisclosed sequence was an essential part of the protein's description. See, *Capon v. Eshhar v. Dudas,* (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078. Likewise, in the instant application, the specification need not provide express guidance with respect to the sequence/domains in Phl p 1 species.
>
> With respect to the variant sequences, reference is made to several art publications which exemplify the various methods and high level of skill in the art that existed at the time the present application was filed for identifying such molecules. These references provide ample evidence that routine protocols for epitope mapping were available and being employed in a variety of fields prior to and at the time of the filing of the present application. For example, Livingstone et al. (Ann. Rev. Immunol., vol. 5,477-501, 1987) describe routine methods for identifying T cell epitope and provide models for predicting T cell epitopes in a protein on the basis of the primary sequence alone.
>
> Moreover, synthesis of large arrays of unique peptides and use of such libraries for screening variants was routine in the art. For example, Geysen (PNAS, 81, 3998-4002. 1984) describes a method, subsequently referred to as "the pin method" or "the Pepscan method", which allows for the rapid, concurrent synthesis on polyethylene rods of hundreds of peptides of sufficient purify for ELISA assays. The screened peptides were mapped to eptitopes of foot-and mouth disease virus coat protein involved in antibody binding. Subsequent publications by the same author expressly account for the routineness of the procedure. "The current methodology requires only basic skills in organic chemistry, and can be used to

synthesize more than 2000 peptides (hexapeptides) per 10 working day." Geysen et al. further state their group "presently tests about 4000 peptides each working day." See, Geysen et al., J. Immunol. Methods, 259-274, 1987. Van der Zee et al. (Eur. J. Immunol. 1989. 19:43-47) modified the Pepscan method so that the synthetic peptides could be released from the solid phase support, for direct use in T cell stimulation assays. Van der Zee used this modified technique to finely map a T- cell epitope in the mycobacterial 65 kDa heat shock protein. Likewise, Maeji et al. used the Pepscan methodology to map T cell epitopes of tetanus toxin (Maeji, N.J., Bray, A.M., Geysen, H.M., Multi-pin peptide synthesis strategy for T cell determinant analysis. J. of Immunol. Methods, 134, 23-33. 1990). Since 1993, the Pepscan technique has been made commercially available in kit form by Cambridge Research Biochemicals, Cambridge, UK. For example, Cason et al. used the Pepscan kit to map immunodominant epitopes of the bovine papillomavirus major (L1) capsid protein. (J. Gen. Virol., 74, 2669-2677, 1993). Likewise Ebner et al. utilized the Pepscan method to identify multiple T cell epitopes on the major birch pollen allergen Bet vl. (J. of Immunol., 150, No.3, 1047-1054. 1993).

In addition to the Pepscan method, Houghten taught a method for synthesizing large numbers of peptides on standard, amino acid resin that was sealed in packets (the "teabag" method). See, Houghten et al., PNAS, 82, 5131-5135, 1985. Using this method, the synthetic peptides could be easily cleaved from the resin allowing them to be used in liquid phase assays. Houghten used this method to simultaneously synthesize 248 different peptides from the influenza hemagglutinin protein (HA1), which were then used to map amino acids involved in the binding of anti-HA1 antibody. Houghten further states that his technique is simple and can be used to perform greater than 1000 syntheses simultaneously. Ofiung et al. utilized the method of Houghten to map human T cell epitopes on the Mycobacterium tuberculosis 65-kilodalton protein antigen. (J Immunol., 141, 2749-54, 1988). As an alternative to protein synthesis, the generation of peptides from a known protein sequence could have been achieved by genetic manipulation of nucleic acid molecules encoding the protein of interest. Relevant techniques include, for example, the use of frequently and non-frequently cutting, restriction enzymes to generate fragments of a nucleic acid molecule encoding the protein of interest; the use of timed exonuclease III and/or Dnase I digestions of a nucleic acid molecule encoding the protein of interest; and the use of the polymerase chain reaction to generate precise fragments of the open reading frame encoding the protein of interest. All of these techniques were being employed at the time of filing. The methodology for performing the aforementioned techniques is further provided in rich detail in Methods in Molecular Biology, vol. 66, Epitope Mapping Protocols, 1996. Not only was it possible to easily generate a multitude of peptides from a known protein, but techniques for high-volume screening of such fragments and peptides for T cell epitopes were clearly available. For instance, such screening could have been achieved by measuring T-cell proliferation in response to peptides in combination with antigen presenting cells. Many of the references already mentioned describe such assays. For example, the aforementioned Van der Zee, Ebner, Ofung, and Lamb references, all teach assays H using 3 -thymidine uptake by T cells as a way of measuring cell proliferation. Methods for assaying large number of samples, for example, employing a 96-well micro-plate, are also provided. It should be noted that plates having a higher density of wells (e.g., 384 wells) along with the use of automated readers capable of handling such platforms were available to the skilled worker as of the filing date of the instant application. In addition, several methodologies were being used to increase the efficiency of such screening and/or isolation of peptides of interest.

Accordingly, it is respectfully submitted that at the time the present application was filed, routine methods were available to screen for specific epitopes and to test the effects contributed by the addition of each amino acid residue to a given epitope. For example, Focke et al. 2001 (cited in the Office Action) disclose Phi p 1 IgE eptitopes and the functional background of generating peptides with reduced IgE reactivity (for example the destruction or deletion of IgE epitopes). Also Schramm et al. 1999 (see specification on page 3, first paragraph) disclose mutated recombinant allergens in which IgE eptiopes are specifically deleted without impairing the T cell eptitopes, which are essential for therapy.

Claims directed to the pharmaceutical composition/vaccines

In the paragraphs bridging pages 5 and 6, the Office Action alleges that the pharmaceutical compositions are non-enabled. This contention is respectfully traversed.

At the outset, Applicants courteously submit that the Office Action fails to present any evidence which suggests the pharmaceutical compositions, as claimed herein, are not enabled. In the absence of such evidence, the rejection is deficient under controlling case law.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, *In re Marzocchi,* 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, Applicants' specification teaches that compounds of the present invention are useful for practicing the methods claimed herein. See, for example, page 5, lines 20-24 and page 20, lines 19-21 of the instant specification, as originally filed. In this regard, Applicants' specification expressly teaches that substituted hypoallergenic forms of allergens can be utilized as pharmaceutical compositions or vaccines. Rationale for the use of the compounds of the instant invention in the desensitization of a subject suffering from allergy is also provided. See, the paragraph bridging pages 1 and 2 of the specification, as originally filed.

In relation to an enabling disclosure on the utilization of Phl p 1 polypeptides as a pharmaceutical composition, the Examiner is courteously invited to review the disclosure contained in the Examples of the present application. For example, in Example 2 (page 17), Applicants' specification provides a disclosure of enzyme allegro sorbent test (EAST) for quantification of IgE binding to the claimed molecules. See, the disclosure in Fig. 3 and the description thereof at page 5 of the instant specification. Moreover, the disclosure in page 3, ~[1 of Applicants' specification and the cited Schramm reference expressly teach that the use of hypoallergenic peptide molecules, such as the rPhl p 1 variant polypeptide of the present invention, for therapy of allergic diseases was appreciated by one of ordinary skilled in the art. To this end, the Examiner is also cordially requested to review the "Immunization" section of Focke et al and the immunoglobulin reactivity data provided in Figs. 5 and 6 and Tables 3-5 of the cited reference.

Thus it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the Phl pl polypeptides of the instant invention. Therefore, the specification's express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO's contentions regarding non-enablement based on the "unpredictability" and "lack of working examples" are especially weak in view of the detailed disclosure contained in Applicants' own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ~[1, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested, if there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below. "

It remains the Examiner's position that when referring to a specific position in a known or unknown polypeptide by number, the specific reference sequence must be also recited because without that recitation the claim has no meaning. Further, the claims are directed to variants and

encompass polypeptides that are not taught in the prior art as being Phl p 1 sequences. Therefore, it is not preferable to omit the wild type reference sequence in the instant claims, as argued my Applicant. Applicant's argument that the specification need not provide express guidance with respect to the sequence/domains in Phl p 1 species is contrary to the enablement and written description requirements as there must be a demonstrated structure function relationship disclosed.

It is the Examiner's position that it would require undue experimentation to produce any and all of the essentially limitless variants encompassed by the instant claim recitation. Further, it would require undue experimentation to determine which of those variants can be used as a diagnostic and/or therapeutic. Experimental use as a research tool is not a sufficient use for the disclosed variants. Rather, they must be able to be used for the specific, defined diagnostic and therapeutic purpose disclosed in the specification. There is no guidance as to what variants other than the variant of SEQ ID NO:2 that can be used for this disclosed purpose.

It also remains the Examiner's position that there is no guidance in the specification on how the allergen variants can be used in vivo as a pharmaceutical composition and/or vaccine. The state of the art is highly unpredictable with regard to successful strategies to induce allergen-specific tolerance. In particular, Larche et al. teaches that the art of allergen-specific immunotherapy is highly unpredictable (Reference U, PTO-892). Though the art is hopeful that antigen-specific immunotherapy techniques will be increasingly successful in treating and preventing allergies in the future, the last 100 years have been devoted to improving the art. One particular problem that has relevance to the instant invention is that the use of native or

recombinant 'native' allergens for allergen-specific immunotherapy carries the risk of adverse allergic events. In the alternative, If IgE binding is successfully reduced by the allergens, some potential problems are that the loss of IgE binding might reduce the uptake of allergen by tolerance-promoting dendritic cells that present FcεRI-bound IgE or competitive antibody classes of the same specificity might be less efficient in the absence of IgE specific epitopes. Therefore, the art recognizes that induction of desensitization and/ or tolerance to a specific allergen by any allergen-specific immunotherapy is highly unpredictable.

11. Claims 1, 4-6, 12-15 and 17 stand rejected and claims 22-23 *are* rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a Phl p 1 allergen mutant consisting of SEQ ID NO:2.

Applicant is not in possession of: a **polypeptide variant of the major allergen Phl p 1 from timothy grass**, which comprises **an additional Cys residue compared with the wild type Phl p 1 sequence** wherein the location of **said additional Cys residue** is higher than amino acid position 230 of said **wild type Phl p sequence** of claim 1; wherein the **additional Cys residue** is located between amino acid positions 230 and 240 of claim 4; wherein the **additional Cys residue** originates from **an amino acid exchange** of claim 5; the **polypeptide variant variant rPhl p 1-A236C** according to claim 1, which comprises a polypeptide sequence set forth in SEQ

ID NO:2, wherein the additional Cys residue has been introduced by exchange of Ala 236 of claim 6; The **polypeptide variant** of claim 1 which exists in various fold forms of claim 12; A fold form rPhl p 1-LM of the **polypeptide variant** according to claim 1, which is obtainable by (a) overexpressing in a host organism, a fusion protein comprising the **rPhl p 1 polypeptide variant** and a His tag; (b) denaturing inclusion bodies isolated from the host organism using guanidinium chloride; (c) renaturing of the dissolved protein on a chelate affinity chromatography column; (d) removing of the His tag, (e) employing gel filtration, (f) further purifying using chelate affinity chromatography, (g) isolating of the target protein from the flow-through; and (h) further employing gel filtration of claim 13; Fold form rPhl p 1-HM of **the allergen variant according** to claim 1 obtainable by (a) overexpressing in a host organism, a fusion protein comprising **the rPhl p 1 polypeptide variant** and a His tag; (b) denaturing inclusion bodies isolated from the host organism using guanidinium chloride; (c) renaturing of the dissolved protein on a chelate affinity chromatography column; (d) removing of the His tag, (e) employing gel filtration, (f) further purifying using chelate affinity chromatography, (g) eluting the target protein with an imidazole gradient; and (h) further employing gel filtration of claim 14; A vaccine which comprises **the polypeptide variant** according to claim 1 and an acceptable carrier of claim 15; and a pharmaceutical composition comprising **a polypeptides variant** according to claim 1 and a pharmaceutically acceptable carrier of claim 17; a **polypeptide variant** of major allergen Phl p 1 from timothy grass which comprises an additional Cys residue compared to the **wild type Phl p 1 sequence**, wherein the location of said additional Cys residue is higher than amino acid position 140 of said **wild-type sequence** of claim 22; which is (a) polypeptide which is encoded by a polynucleotide comprising the sequence set forth

in SEQ ID NO:1; or (b) a polypeptide which comprises the sequence set forth in SEQ ID NO:2 for the same reasons as set forth in the Office Action mailed on 10/09/2007.

Applicant's arguments filed on 04/09/2008 have been fully considered, but are not found persuasive.

Applicant argues:

> "At the outset, it is respectfully submitted that the lack of enablement rejection with respect to the variant of Phl p 1 is moot in view of the aforementioned arguments and/or amendments. With respect to variants of the claimed polypeptides, the PTO's contention is respectfully traversed. Applicants' specification, further in view of the art knowledge of Phl p 1 allergens and sequences (as substantiated by the references cited therein), provides a detailed description of the structure/activity of the claimed molecules. Structures (for example, amino acid sequences) of the claimed Phl p 1 species are recited in the instant sequence disclosure, further in view of the references cited in page 3 of the present specification. See, for example, the cDNA/polypeptide sequences disclosed in aforementioned reference by Petersen et al. It is now well-settled that a specification need not disclose, and preferably omits, what is well known to those skilled in the art when an application is filed (for example, with respect to the sequence of Phl p 1 species and/or variants thereof). See, e.g., *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). See, also, MPEP §2164.05(a). Indeed, the Federal Circuit found that an application, which failed to disclose the amino acid sequence of a claimed protein, was not deficient in the written description requirement, despite the fact that the undisclosed sequence was an essential part of the protein's description. See, *Capon v. Eshhar v. Dudas,* (Fed. Cir. 2005) 418 F.3d 1349, 76 U.S.P.Q.2d 1078. Likewise, in the instant application, the specification need not provide express guidance with respect to the sequence/domains in Phl p 1 species.
>
> With respect to the variant sequences, reference is made to several art publications which exemplify the various methods and high level of skill in the art that existed at the time the present application was filed for identifying such molecules. These references provide ample evidence that routine protocols for epitope mapping were available and being employed in a variety of fields prior to and at the time of the filing of the present application. For example, Livingstone et al. (Ann. Rev. Immunol., vol. 5,477-501, 1987) describe routine methods for identifying T cell epitope and provide models for predicting T cell epitopes in a protein on the basis of the primary sequence alone.
>
> Moreover, synthesis of large arrays of unique peptides and use of such libraries for screening variants was routine in the art. For example, Geysen (PNAS, 81, 3998-4002. 1984) describes a method, subsequently referred to as "the pin method" or "the Pepscan method", which allows for the rapid, concurrent synthesis on polyethylene rods of hundreds of peptides of sufficient purify for ELISA assays. The screened peptides were mapped to eptitopes of foot-and mouth disease virus coat protein involved in antibody binding. Subsequent publications by the same author expressly account for the routineness of the procedure. "The current methodology requires only basic skills in organic chemistry, and can be used to synthesize more than 2000 peptides (hexapeptides) per 10 working day." Geysen et al. further state their group "presently tests about 4000 peptides each working day." See, Geysen et al., J. Immunol. Methods,

259-274, 1987. Van der Zee et al. (Eur. J. Immunol. 1989. 19:43-47) modified the Pepscan method so that the synthetic peptides could be released from the solid phase support, for direct use in T cell stimulation assays. Van der Zee used this modified technique to finely map a T- cell epitope in the mycobacterial 65 kDa heat shock protein. Likewise, Maeji et al. used the Pepscan methodology to map T cell epitopes of tetanus toxin (Maeji, N.J., Bray, A.M., Geysen, H.M., Multi-pin peptide synthesis strategy for T cell determinant analysis. J. of Immunol. Methods, 134, 23-33. 1990). Since 1993, the Pepscan technique has been made commercially available in kit form by Cambridge Research Biochemicals, Cambridge, UK. For example, Cason et al. used the Pepscan kit to map immunodominant epitopes of the bovine papillomavirus major (L1) capsid protein. (J. Gen. Virol., 74, 2669-2677, 1993). Likewise Ebner et al. utilized the Pepscan method to identify multiple T cell epitopes on the major birch pollen allergen Bet vl. (J. of Immunol., 150, No.3, 1047-1054. 1993).

In addition to the Pepscsan method, Houghten taught a method for synthesizing large numbers of peptides on standard, amino acid resin that was sealed in packets (the "teabag" method). See, Houghten et al., PNAS, 82, 5131-5135, 1985. Using this method, the synthetic peptides could be easily cleaved from the resin allowing them to be used in liquid phase assays. Houghten used this method to simultaneously synthesize 248 different peptides from the influenza hemagglutinin protein (HA1), which were then used to map amino acids involved in the binding of anti-HA1 antibody. Houghten further states that his technique is simple and can be used to perform greater than 1000 syntheses simultaneously. Ofung et al. utilized the method of Houghten to map human T cell epitopes on the Mycobacterium tuberculosis 65-kilodalton protein antigen. (J Immunol., 141, 2749-54, 1988). As an alternative to protein synthesis, the generation of peptides from a known protein sequence could have been achieved by genetic manipulation of nucleic acid molecules encoding the protein of interest. Relevant techniques include, for example, the use of frequently and non-frequently cutting, restriction enzymes to generate fragments of a nucleic acid molecule encoding the protein of interest; the use of timed exonuclease III and/or Dnase I digestions of a nucleic acid molecule encoding the protein of interest; and the use of the polymerase chain reaction to generate precise fragments of the open reading frame encoding the protein of interest. All of these techniques were being employed at the time of filing. The methodology for performing the aforementioned techniques is further provided in rich detail in Methods in Molecular Biology, vol. 66, Epitope Mapping Protocols, 1996. Not only was it possible to easily generate a multitude of peptides from a known protein, but techniques for high-volume screening of such fragments and peptides for T cell epitopes were clearly available. For instance, such screening could have been achieved by measuring T-cell proliferation in response to peptides in combination with antigen presenting cells. Many of the references already mentioned describe such assays. For example, the aforementioned Van der Zee, Ebner, Ofung, and Lamb references, all teach assays H using 3 -thymidine uptake by T cells as a way of measuring cell proliferation. Methods for assaying large number of samples, for example, employing a 96-well micro-plate, are also provided. It should be noted that plates having a higher density of wells (e.g., 384 wells) along with the use of automated readers capable of handling such platforms were available to the skilled worker as of the filing date of the instant application. In addition, several methodologies were being used to increase the efficiency of such screening and/or isolation of peptides of interest.

Accordingly, it is respectfully submitted that at the time the present application was filed, routine methods were available to screen for specific epitopes and to test the effects contributed by the addition of each amino acid residue to a given epitope. For example, Focke et al. 2001 (cited in the Office Action) disclose Phi p 1 IgE epitopes and the functional background of generating peptides with reduced IgE reactivity (for example the destruction or deletion of IgE epitopes). Also Schramm et al. 1999 (see specification on page 3, first paragraph) disclose mutated recombinant allergens in which IgE optiopes are specifically deleted without impairing the T cell eptitopes, which are essential for therapy.

Claims directed to the pharmaceutical composition/vaccines

In the paragraphs bridging pages 5 and 6, the Office Action alleges that the pharmaceutical compositions are non-enabled. This contention is respectfully traversed.

At the outset, Applicants courteously submit that the Office Action fails to present any evidence which suggests the pharmaceutical compositions, as claimed herein, are not enabled. In the absence of such evidence, the rejection is deficient under controlling case law.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, Applicants' specification teaches that compounds of the present invention are useful for practicing the methods claimed herein. See, for example, page 5, lines 20-24 and page 20, lines 19-21 of the instant specification, as originally filed. In this regard, Applicants' specification expressly teaches that substituted hypoallergenic forms of allergens can be utilized as pharmaceutical compositions or vaccines. Rationale for the use of the compounds of the instant invention in the desensitization of a subject suffering from allergy is also provided. See, the paragraph bridging pages 1 and 2 of the specification, as originally filed.

In relation to an enabling disclosure on the utilization of Phl p 1 polypeptides as a pharmaceutical composition, the Examiner is courteously invited to review the disclosure contained in the Examples of the present application. For example, in Example 2 (page 17), Applicants' specification provides a disclosure of enzyme allegro sorbent test (EAST) for quantification of IgE binding to the claimed molecules. See, the disclosure in Fig. 3 and the description thereof at page 5 of the instant specification. Moreover, the disclosure in page 3, ~[1 of Applicants' specification and the cited Schramm reference expressly teach that the use of hypoallergenic peptide molecules, such as the rPhl p 1 variant polypeptide of the present invention, for therapy of allergic diseases was appreciated by one of ordinary skilled in the art. To this end, the Examiner is also cordially requested to review the "Immunization" section of Focke et al and the immunoglobulin reactivity data provided in Figs. 5 and 6 and Tables 3-5 of the cited reference.

Thus it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the Phl pl polypeptides of the instant invention. Therefore, the specification's express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO's contentions regarding non-enablement based on the "unpredictability" and "lack of working examples" are especially weak in view of the detailed disclosure contained in Applicants' own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ~[1, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested, if there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below. "

It is the Examiner's position that the specification has only disclosed the Phl p 1 polypeptide variant consisting of SEQ ID NO:2. Applicant has not adequately described any Phl p 1 variant having an additional Cys residue other than SEQ ID NO:2. The term "variant" encompasses any Phl p 1 polypeptide having any number of deletions, substitutions and deletions

and the specification has not adequately disclosed such a genus of polypeptides for use in the claims invention. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" Ex *parte Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007)), at page 16.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Focke et al. (PTO-892, Reference U).

Focke et al. teaches a variant of Phl p 1 (Phl p 1 peptide) with an additional cysteine residue compared with the wild type wherein the additional Cys residue is located in a higher position than amino acid position 140 (In particular, page 3, 'Synthesis, purification and characterization of peptides' section, Figure 1, whole document).

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 16, 2008
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